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Searching for new care models for chronic kidney disease

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Chronic kidney disease is associated with increased death risk. The estimated size of this high-risk population is too large for effective care to be delivered by nephrologists alone and will require models of care delivery that include partnerships with primary-care physicians and incorporate physician extenders. Studies show that some of these care models provide outcomes similar to those seen with nephrologists as sole providers; whether they are cost-effective or improve satisfaction with care remains to be demonstrated.

Kidney International (2012) **82,** 621–623. doi:10.1038/ki.2012.162

The estimates of the prevalence of chronic kidney disease (CKD) in the developed world are staggering. In the United States, more than 13% of adults are thought to have CKD, and more than 15 million people are estimated to have stage 3 CKD.[1] It is also now well established that the risk of death primarily from cardiovascular causes for many people with CKD is much greater than that of progression of disease to end-stage renal disease.[2] Thus, cardiovascular risk reduction is as central to the management of CKD as is slowing the progression of disease. Advances that have been made in the care of these patients include better definitions for staging of CKD, improved guidelines for referral to a specialist, and a better understanding of risk factors associated with higher cardiovascular risk. However, there are two enormous challenges that limit our ability to provide effective care for CKD. First, the size of the CKD population is too large for effective mitigation of cardiovascular risk and slowing of progression of disease to be achieved by nephrologists alone. Second, targets for cardiovascular risk factor modification for people with CKD are largely based on observational data, as there is a paucity of high-level clinical trial evidence. Thus, there is a compelling need not only to develop cost-effective care models that incorporate other health-care providers in the delivery of care to this high-risk population but also to develop high-level evidence to better define therapeutic targets.

Van Zuilen *et al.*[3] (this issue) address this important topic in the presentation of the results of the MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) study. The investigators randomized 788 subjects with CKD (estimated creatinine clearance 20–70 ml/min), including 110 people with a functioning renal transplant, to standard care by a nephrologist or intensive support by a nurse practitioner. Both groups were educated on care guidelines, which consisted of four areas of lifestyle modification (physical activity, nutrition counseling, weight reduction, and smoking cessation), achievement of therapeutic targets for 11 putative risk factors (Table 1), and maximization of the use of four groups of medications (statins, inhibitors of the renin–angiotensin system, active vitamin D, and aspirin).[3] During the mean follow-up of 4.62 years, intensive nurse practitioner support was associated with small but significant improvements in blood pressure control, low-density lipoprotein cholesterol levels, and urine protein excretion, hemoglobin levels were higher, and there was a greater use of antihypertensive medications, statins, active vitamin D, and aspirin. There was, however, no difference in the ability of two treatment approaches to achieve lifestyle modification. More importantly, the small improvements in risk factor control did not translate into a reduction in risk in the composite outcome of myocardial infarction, ischemic stroke, or cardiovascular death.[3] Furthermore, there was no difference in the rate of progression to end-stage renal disease.[3]

This study is very important for understanding how best to develop novel care models for management of people with CKD. There are two potential reasons for the investigators to have been unable to reject the null hypothesis. As the results of the study suggest, intensive support by nurse practitioners may be no better than good care by nephrologists alone. Alternatively, the investigators may have selected risk factors and/or therapeutic targets that were inappropriate, or the magnitude of change achieved may not have been sufficient to affect the outcomes.

Care models that incorporate nurse practitioners are increasingly being used in many parts of the world for the management of chronic diseases such as congestive heart failure and diabetes mellitus.[4] Given the demonstrable success in other fields, the large size of the at-risk population, and the limited availability of trained nephrologists for the number of patients, it is prudent to test care models for CKD in which physicians partner with nurse practitioners to deliver care. In testing such care models, success could be defined in more than one way. Unquestionably, if the intensive care with the support of nurse practitioners results in tangible improvement in 'hard' outcomes such as major adverse cardiovascular events, or all-cause mortality, or progression to end-stage renal disease, the model would be deemed successful. However, to date there is no evidence to support such a claim. While the MASTERPLAN study showed

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Table 1 | Evidence for the importance of risk factors targeted in the MASTERPLAN study to reduce cardiovascular risk in CKD patients

Therapeutic target	Association plausible with CVD in CKD	Epidemiologic evidence linking risk factor to CVD in CKD	Modifiable	RCT evidence that modification reduces CVD risk
Blood pressure	Yes	J-shaped	Yes	No
Urinary protein excretion	Yes	Yes	Yes	No
LDL cholesterol	Yes	No; lower death risk with higher cholesterol or no association	Yes	Yes
Hemoglobin	Yes	Yes	Yes	Increased risk with higher targets
Glycemic control	Yes	Inconsistent	Yes	No
Serum phosphorus	Yes	Yes	Yes	No
Serum parathyroid hormone	Yes	Inconsistent	Yes	No
Urinary sodium excretion	Yes	No	Yes	No
Obesity	Yes	Lower death risk with larger body size	Yes	No
Physical exercise	Yes	Yes	Yes	No
Smoking	Yes	Yes	Yes	No

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; RCT, randomized controlled clinical trial.

small improvements in risk factor control, there was no tangible effect on 'hard' medical outcomes.[3] In another randomized controlled clinical trial ($n = 474$), there was no difference in risk factor management for CKD patients with intensive care coordinated by a nurse; however, the follow-up was too short to ascertain the effect on 'hard' outcomes.[5] Conversely, in a single-center retrospective study, incident dialysis patients followed in a clinic including a nurse practitioner had higher hemoglobin and serum albumin levels, a greater likelihood of having a functioning permanent access, and, in the first year of renal replacement therapy, fewer hospitalizations.[6] Given the mixed bag of evidence, the case that incorporating nurse practitioners improves clinical outcomes in kidney disease has not been convincingly made thus far.

One of the premises for the use of physician extenders in the delivery of care for chronic diseases is that they are amenable to treatment with a limited number of standardized protocols. This necessitates a common disease pathway and common areas of risk factor management in an easily identifiable group. CKD does meet some of these characteristics. Despite the heterogeneous etiology of kidney disease, there are common pathways of hyperfiltration, tubulointerstitial injury, and systemic abnormalities (namely anemia, mineral metabolism, metabolic acidosis) that ensue.[7] However, important differences also exist. Those with overt proteinuria may have greater benefits with the use of inhibitors of the renin–angiotensin–aldosterone system. Despite these advantages, our ability to ameliorate cardiovascular risk depends on targeting the appropriate risk factors. Unfortunately, there is a paucity of high-level evidence regarding cardiovascular risk in CKD populations. In the MASTERPLAN study, the investigators selected four targets for lifestyle modification and 11 putative risk factors and chose to maximize use of four therapeutic agents.[3] It is biologically plausible that the risk factors selected in the study increase cardiovascular risk, and virtually all of them are potentially modifiable (Table 1). However, the epidemiologic evidence linking many of these risk factors with cardiovascular outcomes is either inconsistent or converse of what is seen in the general population (Table 1). Moreover, except for lipid lowering with statins, there is no clinical trial evidence that favorably modifying risk factors mitigates cardiovascular risk (Table 1).[8] To the contrary, there is evidence that attempts to modify one of the risk factors selected in this study—to normalize hemoglobin levels—may increase cardiovascular risk in people with CKD.[9] It is, thus, important to consider that the inability of the MASTERPLAN study to demonstrate benefit with intensive care may conceivably be more a reflection of the risk factors that they selected and the therapeutic targets they set than of the efficacy of the care model with nurse practitioners. Furthermore, patients with a functioning transplant have unique needs arising from acute and chronic rejection, and use of immunosuppressive medications, including glucocorticoids. It is possible that the study of a heterogeneous CKD population that included transplant recipients may have further limited the ability of the study to reject the null hypothesis.

Another threat to the external validity of the study is the occurrence of 'contamination bias' introduced by the education of both groups of health providers to the therapeutic targets. Consequently, though intensive care resulted in statistically significant improvement in the control of some risk factors and increased the use of some selected drugs, the differences from the control group were small and of questionable clinical significance. Juxtaposing this small difference with the very large benefit (50% risk reduction) considered in the power calculations, the study was clearly underpowered to demonstrate lower risk for reaching the primary outcome.

Despite the lack of effect on 'hard' outcomes, nurse practitioner care would be equally valuable if similar care could be delivered but at a lower cost. It would appear at first glance that an increasing use of nurse practitioners would be

cost-effective. At least one previous study has suggested such an economic benefit with the use of nurse practitioners.[5] Whether it indeed was the case in the MASTERPLAN study, however, is unclear. Patients randomized to intensive care had significantly more visits to the health-care facility (7.2 vs. 4.7); however, there were significantly fewer visits to a nephrologist (2.8 vs. 3.7).[3] It is imperative that future studies incorporate cost-effectiveness analyses to evaluate care models using nurse practitioners more comprehensively. Alternatively, nurse practitioner care could be valuable if they focused on aspects of care different from those dealt with by nephrologists and/or if their mandate were more limited than what was attempted in the MASTERPLAN study. Physician visits are often rushed without insufficient time to fully address each aspect of care, and nurse practitioners could supplement areas where care is beleaguered.

In conclusion, the MASTERPLAN trial is a very important study, and both its successes and its failures will inform decision making for the inevitable development of care models that incorporate physician extenders in the care of the high-risk CKD population. The future success of these care models depends on our ability to develop high-level evidence to correctly identify risk factors to be targeted to mitigate cardiovascular risk and disease progression, determine the correct division of labor, and ensure that such care is cost-effective.

DISCLOSURE

Anuja Shah is supported by a research grant from Genzyme. Rajnish Mehrotra has received grant support and/or honoraria from Amgen, Baxter Healthcare, DaVita, Mitsubishi, Shire, Takeda, and Vifor.

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The risks of vascular access

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Fatal vascular access hemorrhage is considered a rare complication of hemodialysis (HD). Ellingson *et al.* indicate otherwise, and their data suggest that it causes 0.4–1.6% of deaths in US HD patients. It is more common with grafts than fistulas, and many victims have had previous access hemorrhages. The widespread presumption that a fistula is the best, and a cuffed catheter the worst, access for HD patients needs reassessment, particularly in older, sicker patients.

Kidney International (2012) **82,** 623–625. doi:10.1038/ki.2012.181

Most nephrologists with any experience of hemodialysis (HD) will have seen cases of severe vascular access hemorrhage requiring urgent surgical intervention, and some will recall fatalities. However, it is likely that most would consider this complication a rare cause of death, and, until now, there has been little in the literature to suggest otherwise. For this reason, the paper by Ellingson *et al.*[1] (this issue) is both surprising and important. The investigators from the Centers for Disease Control and Prevention became involved when a cluster of such deaths was noticed in Maryland, Virginia, and the District of Columbia. A regional investigation identified 88 fatal vascular access hemorrhage (FVAH) deaths over a 6–year period and noted that only a quarter of these cases had been identified on Centers for Medicare and Medicaid Services (CMS) death reports. Across the United States, a startling 1654 deaths were identified from CMS data in the same period, accounting for 0.4% of all HD deaths. However, if the same underestimation had occurred nationwide, the true number of HD deaths due to FVAH might be more than 6000, corresponding to at least 1000 annually or 1.6% of all HD deaths.

The authors then investigated 88 cases in detail and made important observations. A large majority of the bleeds began in the patient's residence and not in the dialysis unit. More than half involved an arteriovenous graft. The mean age of the patients was only 64 years, and only a very small number of cases appear to have been episodes of 'self-harm'. Compared with case controls, the victims were more likely to have had grafts and to be long-term HD patients, and, most

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